

# Celiac Disease Diagnosis -- Is it Time to Give up Endoscopy?

Alessio Fasano, MD  
Presented at Digestive Disease Week  
May 14-19, 2005

Chicago, Illinois; Tuesday, May 17, 2005 -- Celiac disease was among the featured topics discussed at a clinical symposium presented during this year's Digestive Disease Week meeting that focused on the role of serologic testing as a noninvasive tool for the diagnosis of gastrointestinal disorders.<sup>[1]</sup> Celiac disease is an immune-mediated enteropathy triggered by the ingestion of gluten-containing grains (including wheat, rye, and barley) in genetically susceptible individuals. A well-attended session with an engaged audience discussed the state of the art of the currently available diagnostic tools, their strengths, and their pitfalls.

## Epidemiology: The "Global Village" of Celiac Disease

The general perception that celiac disease is rare outside the European continent was, until recently, unsubstantiated by any large epidemiologic study. This controversy has been put to rest by a series of recent reports<sup>[2]</sup> and by a large multicenter study conducted in the United States<sup>[3]</sup> suggesting that celiac disease is as frequent in the "new continent" (prevalence in the general population of 1:133) as in Europe. The bottom line is that if you search for it, you will find it.

## Clinical Presentation -- Not Only Intestine

Celiac disease can manifest with a previously unappreciated range of clinical presentations, including the typical malabsorption syndrome (chronic diarrhea, weight loss, abdominal distension) affecting children, as well as with a spectrum of symptoms potentially involving any organ system.<sup>[4]</sup> Recent epidemiologic studies showed that adult-onset, extraintestinal forms of celiac disease are much more frequent than classical pediatric forms of the disease.<sup>[5]</sup> Because celiac disease often presents in an atypical or even silent manner, many cases remain undiagnosed and carry the risk of long-term complications, including osteoporosis, infertility, neurologic disorders, or cancer.

## Diagnosis -- From Stool Testing to Genomics

Diagnosis of celiac disease depends on the use of serologic markers in conjunction with an intestinal biopsy (during endoscopy). Until the early 1980s, the diagnostic tools for celiac disease were rudimentary at best, being based on nonspecific tests, including fecal fat, D-xylose absorption, and serum carotene. In the past decade, however, researchers and diagnostic manufacturers have made great strides in developing sensitive and specific assays for this disease, and new genetic and protein markers hold even more promise for the future.<sup>[1,6]</sup>

Commercially available serologic tests include tests for anti-gliadin IgA and IgG antibodies, anti-endomysium IgA antibodies, and for anti-tissue transglutaminase (tTG) IgA and IgG antibodies. In the clinical setting, where patients have been identified on the basis of symptoms, the serologic tests have been evaluated as a single test, a combination of tests, or in the setting of sequential use of 2 or more tests. Because of the variable and generally inferior accuracy of the anti-gliadin tests and the fact that they cannot distinguish between celiac disease and other gluten reactions (allergy, sensitivity, etc), their use is no longer routinely recommended for identifying individuals with this disease.<sup>[6,7]</sup> The anti-endomysium antibody test is based on an immunofluorescent technique and, therefore, is time-consuming to perform, generally more expensive compared with other tests, and, because the interpretation is operator-dependent, potentially more prone to errors. However, its high specificity makes this test one of the most formidable noninvasive diagnostic tools in gastrointestinal practice. The discovery of tTG as the antigen recognized by the celiac disease-specific anti-endomysium antibodies allowed for the development of an enzyme-linked immunosorbent assay (ELISA)-based test for the detection of specific antibodies (tTG) whose sensitivity and specificity are close to those obtained with the anti-endomysium antibody test. The anti-actin antibody assay represents the most recent addition to the

## Celiac Disease Diagnosis -- Is it Time to Give up Endoscopy?

"diagnostic arsenal" in celiac disease. It was recently reported that this test is particularly sensitive in detecting cases of celiac disease characterized by severe intestinal mucosal damage, with a reported sensitivity of 100%.<sup>[8]</sup> If these data are confirmed, it may be possible to devise a stepwise protocol in which symptomatic patients who test tTG-positive (and subsequently anti-actin antibody positive) can avoid intestinal biopsy for diagnostic confirmation.

On the basis of current evidence and practical considerations, including accuracy, reliability, and cost, measurement of tTG IgA is recommended as the initial test for celiac disease.<sup>[7]</sup> In symptomatic individuals, the positive predictive value of tTG and anti-endomysium antibody assays for finding biopsy evidence of celiac disease ranges from 0.9 to 0.95.<sup>[6]</sup> Nevertheless, given the fact that a diagnosis of celiac disease implies a lifelong commitment to a gluten-free diet, the mainstay of diagnosis remains a small intestinal biopsy showing the typical celiac enteropathy followed by clinical (and, in selected cases, histologic) remission after treatment with the gluten-free diet.<sup>[1,9]</sup>

It is the interplay between genes and gluten that leads to the generation of celiac disease-specific antibodies and the associated histologic damage and symptoms that characterize the disease. Among the various genes, the HLA class II haplotypes DQ2 and/or DQ8 have been identified as absolutely necessary for the development of disease.<sup>[1,10]</sup> Because up to 30% of the healthy population also carries these HLA haplotypes, their presence is not diagnostic for celiac disease -- although their absence essentially rules out the disease. Therefore, the most effective application of HLA testing is in the setting of doubtful or mismanaged cases or in relatives of patients with celiac disease to help guide the decision of whether they need to be followed over time.

The diagnosis of celiac disease is considered definitive when there is complete symptom resolution after treatment with a strict gluten-free diet in a previously symptomatic individual with characteristic histologic changes on small intestinal biopsy. A positive serologic test that reverts to negative after treatment with a strict diet provides further supportive evidence for the diagnosis.<sup>[7]</sup>

### Management -- Don't Abandon Your Patient

Total lifelong abstinence of gluten ingestion remains the cornerstone of treatment for this disease. Therefore, establishing the diagnosis of celiac disease often represents the end of a diagnostic dilemma and the beginning of a management challenge.<sup>[9]</sup> In addition to the involvement of expert nutritionists for implementation of the gluten-free diet, a clear understanding of when and how often follow-up is necessary, and the need to check for possible complications using both established (ie, bone densitometry) or cutting-edge technologies (ie, wireless capsule endoscopy), is also essential. Several studies have suggested that adherence to a gluten-free diet is suboptimal at best (45%-80%).<sup>[9]</sup> Therefore, periodic monitoring of patients with celiac disease, regardless of relapse of symptoms, is necessary to ensure appropriate adherence to the diet. Even if there is no clear evidence regarding the most effective strategy for monitoring patients with celiac disease, measurement of tTG after 6 months of diet implementation and on a yearly basis thereafter seems to be the most reliable indicator of dietary adherence and recovery.<sup>[9]</sup> Measurement of tTG is also recommended in individuals with persistent or recurrent symptoms at any time after starting a gluten-free diet, because an increase in antibody levels suggests dietary noncompliance.

Due to the high morbidity and mortality associated with untreated celiac disease and the prolonged delay in diagnosis in patients in the United States,<sup>[4]</sup> serologic testing of at-risk patients (ie, case finding) should be considered the best strategy for optimizing our current knowledge of celiac disease to alleviate unnecessary suffering, prevent complications, and improve the quality of life of individuals with this disease.

### Concluding Remarks

## Celiac Disease Diagnosis -- Is it Time to Give up Endoscopy?

As should be evident by the discussion above, a high degree of awareness among healthcare professionals and appropriate application of serologic testing can help to identify many atypical cases of celiac disease. Although the gluten-free diet currently remains the cornerstone of treatment, new options may be on the horizon to help enhance the care of individuals with this immune-mediated enteropathy.

### References

1. Fasano A. Sprue: Can serology supplant endoscopic biopsy for diagnosis and monitoring? In AGA Clinical Symposium: Serologic testing for GI diseases: Are non-invasive tests helpful? Program and abstracts of Digestive Disease Week 2005; May 14-19, 2005; Chicago, Illinois. [Sp197]
2. Catassi C, Fasano A., Corazza GR, eds. *The Global Village of Celiac Disease*. Basel, Switzerland: Karger Press; 2005.
3. Fasano A, Berti I, Gerarduzzi T, et al. A multicenter study on the sero-prevalence of celiac disease in the United States among both at risk and not at risk groups. *Arch Int Med*. 2003;163:286-292.
4. Green P. How varied is the clinical presentation of celiac disease? In AGA Clinical Symposium: Celiac disease: a significantly underdiagnosed multisystem disorder. Program and abstracts of Digestive Disease Week 2005; May 14-19, 2005; Chicago, Illinois. [Sp446]
5. Murray JA, Van Dyke C, Plevak MF, Dierkhising RA, Zinsmeister AR, Melton LJ. Trends in the identification and clinical features of celiac disease in a North American community 1950-2001. *Clin Gastroenterol Hepatol*. 2003;1:19-27.
6. Rostom A. Evidence based analysis: What is the true prevalence of celiac disease, and what serological tests are best for diagnosis? In: AGA Clinical Symposium: Celiac disease: a significantly underdiagnosed multisystem disorder. Program and abstracts of Digestive Disease Week 2005; May 14-19, 2005; Chicago, Illinois. [Sp445]
7. Hill I, Dirks MH, Liptak GS, et al. Guideline for the diagnosis and treatment of celiac disease in children: recommendation of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. *J Ped Gastroenterol Nutr*. 2005;40:1-19.
8. Clemente MG, Musu MP, Troncone R, et al. Enterocyte actin antibodies: A new tool in celiac disease diagnosis. *Am J Gastroenterol*. 2004;99:1551-1556.
9. Pietzak M. Appropriate approaches to management. In AGA Clinical Symposium: Celiac disease: a significantly underdiagnosed multisystem disorder. Program and abstracts of Digestive Disease Week 2005; May 14-19, 2005; Chicago, Illinois. [Sp447]
10. Kagnoff M. Role of genes, the environment and the immune system in disease pathogenesis. In AGA Clinical Symposium: Celiac disease: a significantly underdiagnosed multisystem disorder. Program and abstracts of Digestive Disease Week 2005; May 14-19, 2005; Chicago, Illinois. [Sp444]

Printed with permission of Alessio Fasano, M.D.